# LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

## Restenosis after coronary angioplasty: a proposal of new comparative approaches based on quantitative angiography

SIR—We have supported the move away from a categorical approach in the diagnosis of restenosis towards one which recognises the continuous distribution of vessel diameters.[1 2] Serruys *et al*'s calculations of required trial sizes to evaluate possible strategies against restenosis (*British Heart Journal* 1992;**68**:417–24) are, however, based on some assumptions with which we would not necessarily agree. As a general rule, trials that rely on comparison of continuous variables tend to be more powerful than those that rely on categorical distinction because the continuous variables provide more information. In their statistical analysis of lumen diameter, Serruys *et al* concentrated (perhaps too much) on difference in the locations of means and not on the striking difference in variance between the lumen diameters immediately after angioplasty at follow up. It is legitimate to look on restenosis as a process which does in fact increase the expected variability of the vessel diameter in the long term. We should therefore expect that if an effective method of preventing restenosis were to be discovered, it would provide a population not only with a larger mean luminal diameter (MLD), but also with an MLD that was considerably less variable than in the untreated group. We argue that failing to take this into account leads to an unnecessarily pessimistic estimate of the number of cases needed in the a priori design of a restenosis trial. Moreover, ongoing analysis of the pooled variance between treated and untreated groups and its comparison with known data about the variance of lumen diameter in control patients might be a useful way of monitoring the progress of a trial and could be written into the protocol from the start.

Trial design and power calculations should also take into account the magnitude of the effect that would be clinically meaningful rather than simply statistically significant. Most trialists have shown a difference in their placebo group from post PTCA to follow up in the order of 0·4 mm (SD 0·5). Though a 50% reduction in this luminal diameter change from placebo to treated (from a 0·4 mm to 0·2 mm change) will require many fewer patients to show a difference (85 per group for data on a continuous variable, $2p = 0{\cdot}05$, 90% power) this 50% reduction may not, because of the intensity of the biological process, be achievable. Although any predecided percentage reduction will be arbitrary, the agent to be tested has to be clearly worth using. For example a 10% reduction may be easily achievable with a given agent but whether it is clinically worthwhile, especially if the drug has important side effects and may be required for 3–4 months, is debatable. In addition about 2000 patients would be required in each group to show any benefit with an agent that reduced the luminal change by such a small percentage. Maybe we should only be considering agents that are safe and yet powerful enough to reduce the event rate by "a sufficiently large" percentage. The 30% reduction used by the Rotterdam group, which requires 230 patients per group, may fit this criterion but this is also an arbitrary figure. The importance of having a significant impact on angiographic restenosis is supported by the Rotterdam group's own data, which beautifully show a highly non-linear relation between minimal luminal diameter and clinical symptoms. Marginal reduction in restenosis rates may thus have little worthwhile clinical impact.

In conclusion, while we applaud the Rotterdam group for setting standards in measurement in restenosis, we suggest that the following trial model be considered:

- Trial size be determined by assessment of agents that are truly going to have an impact (perhaps nearer a 50% reduction than a 10% reduction in measured effect) with trialists indicating before the start of the trial what they are trying to achieve.
- Realistic models should be developed to monitor progress during trials in order to determine whether changes in placebo and treated group mean and variance values are comparable. This may be better than routinely going through trials, one after another with a stipulated and perhaps arbitrary 234 patients per group.

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1 Gershlick AH, de Bono DP. Restenosis after angioplasty *Br Heart J* 1990;**64**:351–3.
2 Gershlick AH, More RS, Brack MJ, Syndercombe Court D, Balcon R. Angiographic restenosis after angioplasty: comparison of definitions and correlation with clinical outcome *Coronary Artery Disease* 1993;4:73–82.

## Accelerated graft atherosclerosis after heart transplantation

SIR—Two editorials in the *British Heart Journal* reviewed current knowledge of accelerated graft atherosclerosis after heart transplantation (AGA).[1 2] Among the aetiological factors discussed was hyperlipidaemia. The desire to treat hyperlipidaemia in this setting is powerful, and many such patients are so treated, despite a lack of evidence that this is of benefit. The aim of treatment is to retard or prevent AGA. This goal is highly desirable because this disease is the major obstacle to long-term survival after heart transplantation, and occurs in 40–70% of patients within 5 years of transplantation.[2]

Several reports describe the response to drug treatment of hyperlipidaemia in cardiac transplant recipients.[3–5] These have all been retrospective analyses of the effects on lipid concentrations, rather than on the intended disease process. Patient numbers have been small.

Treatment of hyperlipidaemia to reduce AGA is based on two premises: first, that AGA in transplant patients is due (at least in part) to hyperlipidaemia; and secondly, that such treatment is effective in reducing coronary artery disease in the general population.

Evidence relating hyperlipidaemia to the development of AGA has been derived mainly from single centre retrospective analyses of the association of various factors with AGA. A link between hypercholesterolaemia and AGA was indicated by some[6 7] but not all studies.[8] Additional suggestive evidence derives from hypercholesterolaemic animal transplant models, though the applicability of such models to human disease is not certain.

The second premise arises from the application of guidelines for the treatment of hyperlipidaemia within the general population.[3] We believe it is unreasonable to apply these guidelines to transplant patients for two reasons: firstly, AGA is different from native coronary artery disease in terms of its distribution and morphology, histology, and associated risk factors (to the extent that it might be considered to be a separate disease); and secondly, no reduction in mortality has been demonstrated.

The recent reports[3–5] have shown that treatment of hyperlipidaemia in transplant recipients is feasible and can achieve some reduction in cholesterol concentrations; but they and others[9] have shown that serious side effects, particularly rhabdomyolysis and renal failure, are frequent, especially with more aggressive therapy. All of these studies have been too small to address the question of benefit, in terms of clinical or angiographic end points. Thus there is a real possibility that such treatments may be harmful, and the likelihood of benefit remains a matter of conjecture.

We believe that there is insufficient evidence to justify the treatment of hyperlipidaemia in heart transplant recipients and support the proposal[2 3] that a multicentre prospective trial of sufficient size to assess the possible impact of this treatment on AGA should be started without delay.

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6 Barbir M, Banner N, Thompson GR, Khagani A, Mitchell A, Yacoub M. Relationship of immunosuppression and serum lipids to the development of coronary arterial disease in the transplanted heart. *Int J Cardiol* 1991;**32**:51–6.
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## A characteristic continuous wave Doppler signal in cor triatriatum?

SIR—Alwi *et al* (*British Heart Journal* 1992;**68**:6–8) state that "Previous reports in English merely mentioned high velocity diastolic signals when the pulsed Doppler sample volume was placed beneath the restrictive orifice."

This statement is inaccurate. We gave an accurate description of the haemodynamics in this rare anomaly including colour Doppler plates of the exact flow directions in early and late systole and diastole in a case that we reported in 1990.[1]

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1 Glaser J, Goren A, Ilan M, Vidne B. Cor triatriatum sinistrum: Diagnosis by Doppler echocardiography. *Cardiology* 1990;77: 472–6.

## The future of paediatric cardiology in the United Kingdom

SIR,—As chairman of the working party that produced the report on paediatric cardiology (*British Heart Journal* 1992;**68**:630–3) may I make a small but important amendment. This report has been a long time in gestation and I am happy to say that during the last "trimester" paediatric cardiology has been born again in Wales at the University Hospital of Wales in Cardiff. The information regarding paediatric cardiology in Cardiff contained in the report is thus out of date.

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## *Propionibacterium acnes* causing perivalve abscess

SIR,—Dr Horner and colleagues described their experience with a rare case of *Propionibacterium acnes* endocarditis associated with an aortic root abscess.[1] We have recently seen a similar case of prosthetic mitral valve endocarditis with operative evidence of healed perivalvar abscesses and were impressed by certain features common to both cases which are worthy of comment in this rare infection.

A 57 year old woman was admitted to hospital with severe mitral regurgitation and suspected infective endocarditis in August 1992. In 1981 she had undergone mitral valve replacement with a Starr-Edwards prosthesis for rheumatic heart disease. In 1991, eighteen months before admission she had developed progressive dyspnoea and a cough accompanied by a raised erythrocyte sedimentation rate and a mitral regurgitant murmur. One month before admission she also experienced weight loss. Five sets of blood cultures produced a growth of *Propionibacterium acnes*. The patient was clinically stable, but before valve replacement was undertaken satisfactory control of sepsis was desired. Valve replacement was deemed necessary because of the degree of regurgitation observed from this prosthesis. The organism isolated was susceptible to penicillin, ampicillin, vancomycin, and erythromycin and was less susceptible to rifampicin and ciprofloxacin. Minimum inhibitory concentrations were 0·5 mg/l, 0·12 mg/l, 2·0 mg/l, 1·0 mg/l, 2·0 mg/l, and 2·0 mg/l respectively. Thus treatment with benzyl penicillin and gentamicin was started with the aim of later elective valve replacement. The fever resolved but despite satisfactory serum gentamicin concentrations, symptoms of dizziness developed after three weeks' combination therapy. Benzyl penicillin alone (2 MU every four hours) was given until elective replacement of the mitral valve prosthesis was performed a week later. At operation, there were multiple tracts around the original prosthesis and, when it was removed, evidence of healing periannular abscesses with some vegetations. Cultures of the vegetations and prosthesis were sterile. The patient continued to receive benzyl penicillin 2 MU every four hours with the addition of probenecid 500 mg twice daily during convalescence on the ward. Peak and trough serum bactericidal titres were 1/8 and <1/2 respectively. Also, several blood cultures obtained when penicillin concentrations were expected to be at their lowest (that is, just before the penicillin doses) proved to be sterile. However, after three weeks, a classic rash of penicillin allergy developed which necessitated a change in antibiotic therapy to vancomycin. This was continued for a further three weeks with regular monitoring for therapeutic serum concentrations—giving a total of six weeks postoperative intravenous antibiotic therapy. The patient remains well to date.

This case illustrates the typical nature of endocarditis caused by a low grade pathogen—with a relatively long history and minimal signs of infection. In a study of antibiotic prophylaxis, 22 of 60 patients receiving conventional flucloxacillin/aminoglycoside prophylaxis for cardiac surgery had propionibacteria retrieved from the extracorporeal blood reservoir at completion,[2] so contamination is potentially common but infection is rare. Could this infection have been present for 10 years before presentation? The case supports the opinion that perivalve abscess, a more common complication of prosthetic than native valve endocarditis, is not necessarily associated with more virulent microorganisms. Therefore, if the clinical response to optimum antimicrobial therapy is poor or other signs of uncontrolled sepsis are observed, the diagnosis of abscess formation should be suspected even in endocarditis caused by a low grade pathogen. It is noteworthy that healing of the perivalvar abscesses was progressing with four weeks' treatment with intravenous antibiotics in our patient. There are no guidelines on the amount and length of antibiotic therapy that are necessary after removal of an infected prosthetic valve but we, like Horner *et al*, continued this for six weeks. Fear of recurrent infection leads to antibiotic therapy being prolonged. This has important consequences in terms of side effects, toxicity, and cost. Only experience can guide management.

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